REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 1-5, 9-19, and 20-24 are pending; claims 1-5, 9, 20, and 24 are currently under examination and claims 10-19, and 21-23 are withdrawn. Notwithstanding any of the rejections, claim 9 is amended to comply with the requirement that multiple dependent claims refer only in the alternate to the claims from which they depend.

CLAIM OBJECTIONS

The Examiner objected to claims 9 and 20, asserting that these multiple dependent claims do not refer to the other claims in the alternative.

Applicants respectfully traverse this objection. Nonetheless, without acquiescence, claim 9 is amended to recite "[t]he method according to any of claims 1 to 5," which Applicants submit to represent an acceptable multiple dependent format. *See* M.P.E.P. 608.01(n)(I)(A). It is also noted that claim 20 as previously presented already utilizes this acceptable format, likewise reciting "[t]he method according to any of claims 1 to 5."

Applicants submit that the instant multiple dependent claims properly refer in the alternative to the claims from which they depend, and respectfully request withdrawal of this objection.

REJECTIONS UNDER 35 U.S.C. § 103

A. The Examiner rejected claims 1, 2, 5-9, and 20 under 35 U.S.C. § 103(a) for alleged obviousness over Kelly *et al.* (WO 98/08503), supported by Sinha *et al.* (*Photochem. Photobiol. Sci.*, 1:225-236 (2002). The Examiner agrees that Kelly *et al.* do not teach a compound as presently elected, and also agrees that neither Kelly *et al.* nor Sinha *et al.* explicitly teach applying the claimed compounds to the skin after UV exposure, as claimed. The Examiner, however, asserts that it would have been obvious to practice such subject matter in view of the teachings in Kelly *et al.* that the claimed compounds are effective in "scavenging and quenching cellular free radicals," and further in view of the teachings in Sinha *et al.* that free radical formation leads to cyclo-butane dimer (CPD) formation.

B. The Examiner rejected claims 3 and 24 under 35 U.S.C. § 103(a) for alleged obviousness over Kelly *et al.*, supported by Sinha *et al.* The Examiner agrees that Kelly *et al.* fail to teach the *treatment* of skin cancer using the genus of claimed compounds, but asserts that Sinha *et al.* teach that free radical damage which leads to CPD formation leads to skin cancer. The Examiner then asserts that it would have been obvious to combine these teachings with Kelly *et al.* to arrive at a method of *treating* skin cancer.

C. The Examiner rejected claim 4 under 35 U.S.C. § 103(a) for alleged obviousness over Kelly *et al.,* supported by Sinha *et al.* and Fleming *et al.* (*Cancer* 75:S2, 699-704, 1994). The Examiner relies on Kelly *et al.* and Sinha *et al.* as above, agreeing that these references fail to teach skin cancer as being basal cell carcinoma, squamous cell carcinoma, or malignant melanoma. The Examiner, however, asserts that Fleming *et al.* teach that these types of carcinomas represent over 90% of all skin cancers, such that it would have been obvious to arrive at a method for *treating* such skin cancers.

Applicants traverse these rejections and submit that the instant claims satisfy the requirements of non-obviousness over the cited references. As previously made of record, the key to establishing any rejection under 35 U.S.C. § 103 is a clear articulation of reasons why the claimed invention would have been obvious, which should be made explicit by the Examiner. *KSR v. Teleflex*, 550 U.S. at ___, 127 S.Ct. 1727, 1741 (2007), citing *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness cannot be sustained by mere *conclusory statements*; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.") (emphasis added). Here, the Examiner has not adequately demonstrated by the required technical reasoning or evidence that the combination of references relied upon by the Examiner to arrive at the claimed invention would have been expected to yield nothing more than predictable results, based on the knowledge in the art at the time of filing, or, phrased differently, the Examiner has not established by the required technical reasoning that a person of ordinary skill in the art at the time of filing would have modified these references to achieve the claimed invention with a reasonable expectation of success *See, e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,* 491 F.3d 1342, 1360, 1363 (Fed. Cir. 2007).

As one deficiency in the cited references, neither Kelly *et al.* nor Sinha *et al.* teach or suggest each feature of the instant claims. Indeed, as recognized by the Examiner (*see* the Action, page 3), neither of these references teach the active, recited step of topical application of the claimed compounds after UV exposure, so as to promote and/or enhance the rate of repair of UV-induced, DNA mutagenic damage. In addition, as also recognized by the Examiner, neither of these references teach or suggest such topical application for reducing the formation of skin cancer, as recited in claim 3, let alone wherein the skin cancer is basal cell carcinoma, squamous cell carcinoma or malignant melanoma, as recited in claim 4.

Despite these clear deficiencies in the cited references, the Examiner asserts that it would have been obvious to apply the claimed compounds to skin after UV exposure, such as to reduce the formation of skin cancer (*see* the Action, page 3, item 8). Applicants respectfully disagree, and submit that neither Kelly *et al.* nor Sinha *et al.* provide any apparent technical reason for a person of ordinary skill in the art at the time of filing to reasonably predict or expect that applying a compound of Formula I after UV exposure could have been relied upon to reduce DNA mutagenic damage, and thereby reduce the formation of skin cancer. As a first point on this issue, it is respectfully noted that any general reference by the Examiner to Kelly *et al.* regarding the treatment of cancer (*see* the Action, page 4, item 13; page 5, item 16, first and last sentence; page 6, item 21, first and last sentence), based, in part, on the antioxidant activity of the claimed compounds described at that time, is not technically relevant to the application of said compounds after UV exposure, such as to reduce the formation of skin cancer, which is one object of the instant application. For instance, many compounds known for the treatment of cancer, such as taxol or etoposide, would hardly be considered practical or safe for everyday use in reducing the formation of cancer. Indeed, it is submitted that the treatment of cancer, which is typically based on the killing of tumor cells or altering their microenvironment, and the reduction of skin cancer, which, in this case, is based on the enhancing the repair rate of DNA mutagenic damage after UV exposure, often relate to technically distinct mechanisms. Given these technical distinctions, the reference in Kelly *et al.* to the use of the claimed compounds for the treatment of cancer provides no reasonable expectation that such compounds can be used to reduce the formation of skin cancer following UV exposure.

As a further point, the references in Kelly *et al.* to the free radical scavenging and antioxidant activities of the claimed compounds, as relied upon by the Examiner, do not provide a reasonable expectation that such compounds would have had therapeutic utility when applied after UV exposure to enhance the repair rate of DNA mutagenic damage, and thereby reduce the formation of skin cancer. For instance, the LDL Anti-Oxidation Test described at page 32, lines 1-14, of Kelly *et al.*, upon which the Examiner relies for the assertion that the claimed compounds are capable of "scavenging and quenching cellular free radicals" (*see* the Action, page 3, item 8), does not in fact test this property. Rather, this test measures the ability of the tested compounds to "chelate transition metals," such as Cu^{2+}, so as to prevent the oxidation of polyunsaturated fatty acids (PUFAs) present on LDL, as measured by increased lag time before the PUFAs are oxidized to lipid hydroperoxides (*see, e.g.,* page 32, lines 1-7 of the specification; and Esterbauer *et al.*, *Free Rad Res Coms*. 6:67-75, 1989, abstract submitted herewith; and Esterbauer *et al.*, *EXS*. 62:145-57, 1992, abstract submitted herewith). Likewise, the Redox Tests described at page 32, line 20 to page 33, line 17, of Kelly *et al.*, shows that the tested compounds prevent the oxidation of lipids, proteins, and other biological species (*see, e.g.,* page 33, lines 4-5, and line 12 of Kelly *et al.*). In focusing entirely on the prevention of lipid oxidation by the tested compounds, Kelly *et al.* do not necessarily establish that these compounds are capable of "scavenging and quenching cellular free radicals" in the particular manner relied upon by the Examiner, such as by showing that these compounds have the ability to reduce the damage caused by free radicals already present in post-UV exposure skin.

In this regard, it is kindly emphasized that "rejections on obviousness cannot be sustained by mere *conclusory statements*; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added). Here, given the particular nature of the teachings in Kelly *et al.*, as described above, Applicants submit that the Examiner has not explicitly established by the required technical reasoning and evidence the manner in which the prevention of lipid oxidation by certain compounds of Formula I would have provided a reasonable expectation that topical application of these compounds to skin after UV exposure would have had any therapeutic effect on reducing DNA mutagenic damage caused by free

radicals already present in the skin, such as to reduce the formation of skin cancer. Instead, the Examiner provides no technical basis to support the leap from applying the claimed compounds before UV exposure to applying them after UV exposure (*see* the Action, page 3, item 8), which a person skilled in the art understands to relate to entirely different physiological activities. In failing to establish the requisite reasonable expectation of success in this regard, Applicants submit that the Examiner has not satisfied his burden of proof in establishing a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness).

Regardless of the absence of such evidence, Applicants submit that the activity of the tested compounds in preventing lipid oxidation does not reasonably suggest to a person of ordinary skill in the art at the time of filing that such compounds could have been applied after UV exposure to reduce DNA mutagenic damage, and thereby reduce skin cancer formation. As previously made of record, given the timing by which UV-induced free radical formation relates to DNA mutagenic activity, a compound having the sole ability to prevent oxidation would not have been expected to promote or enhance the repair rate of DNA mutagenic damage after UV exposure. As noted by the Examiner, Sinha *et al.* teach that UV-induced free radical formation induces DNA damage through the formation of CPDs (*see* the Action, page 3, item 8). However, as disclosed in the instant specification, CPD formation occurs almost immediately upon UV exposure, representing the earliest indicator of molecular damage following exposure to UV radiation (*see, e.g.,* page 12, line 26 of the specification). But after this immediate step of free radical-induced CPD formation, a compound understood to be capable of little more than preventing lipid oxidation via its antioxidant activity would be expected to have little, if any, further therapeutic effect once a subject is no longer exposed to UV light, such as after UV exposure. In other words, compounds having the particular type of antioxidant activity described in Kelly *et al.* may have been expected to prevent or reduce the formation of free radicals during exposure, *i.e.,* if applied before UV exposure, but once the damage has already occurred and a subject is no longer exposed to UV radiation, *i.e.,* after UV exposure, as recited in the instant claims, such antioxidant compounds would have been expected to contribute little or nothing to the post-UV exposure repair process itself. Thus, a person of ordinary skill in the art at the time

of filing would have had no technical reason to utilize these compounds in the particular fashion claimed by Applicants with a reasonable expectation of success. *See KSR v. Teleflex*, 127 S.Ct. at 1741.

In contrast to the cited references, the instant application provides an apparent, technical reason to topically apply the recited genus of compounds after UV exposure. For instance, as previously made of record, the topical application of the presently claimed compounds after UV exposure relates directly to the newly described and unexpected properties of these compounds, including the ability to enhance the repair rate of damaged DNA, which unexpected properties are not described in either Kelly *et al.* or Sinha *et al.* (*see, e.g.,* Examples 2 and 3 of the instant specification). Absent knowledge of such properties, a person of ordinary skill in the art at the time of filing would have had no technical basis to rely on these compounds in reducing the formation of skin cancer following UV exposure. In view of this understanding, and in view of the deficiencies in Kelly *et al.* and Sinha *et al.*, there is no suggestion to combine and modify the teachings of these references, as advanced by the Examiner, except from using Applicants' invention as a template through a hindsight reconstruction of Applicants' claims. *See Ex Parte Crawford et al.*, Appeal 20064249, Decided May 30, 2007.

Therefore, Applicants submit that the cited references fail to provide either the requisite motivation or the requisite reasonable expectation of success in topically applying the genus of recited compounds after UV exposure to increase the repair rate of UV-induced DNA damage, and thereby reduce the formation of skin cancer. Given the deficiencies in the cited references and the lack of technical reasoning and evidence to support the Examiner's proposed modification of these references, Applicants submit that the instant claims satisfy the requirements of non-obviousness under 35 U.S.C. § 103, and respectfully request withdrawal of this rejection.

Applicants believe that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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Enclosures:

Esterbauer *et al.*, *Free Rad Res Coms*. 6:67-75, 1989, abstract.
Esterbauer *et al.*, *EXS*. 62:145-57, 1992, abstract.

WTC:rp

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